Carbenes

International Edition: DOI: 10.1002/anie.201700045
German Edition: DOI: 10.1002/ange.201700045

Construction of Fused Pyrrolidines and β-Lactones by Carbene-Catalyzed C–N, C–C, and C–O Bond Formations

*Xingxing Wu, Lin Hao, Yuexia Zhang, Maiti Rakesh, Rambabu N. Reddi, Song Yang, Bao-An Song, and Yonggui Robin Chi**

Abstract: *A carbene-catalyzed intermolecular C–N bond formation, which initiates a highly selective cascade reaction for the synthesis of pyrrolidine fused β-lactones, is disclosed. The nitrogen-containing bicyclic β-lactone products are obtained with good yields and excellent stereoselectivities. Synthetic transformations of the reaction products into useful functional molecules, such as amino catalysts, can be efficiently realized under mild reaction conditions. Mechanistically, this study provides insights into modulating the reactivities of heteroatoms, such as nitrogen atoms, in challenging carbene-catalyzed asymmetric carbon–heteroatom bond-forming reactions.*

Heterocycles constitute a major class of organic compounds and are frequently found in synthetic medicines, biomolecules, and natural products. For example, nitrogen-containing heterocyclic motifs, such as pyrrolidines, form the key scaffolds of the natural amino acid proline and numerous biologically active molecules.[1] Oxygen-containing heterocycles, such as β-lactones,[2] have been widely used in assembling both small molecules[3a–d] and polymers.[3e] Examples of fused bicyclic β-lactone-containing natural products with significant biological activities include pancreatic lipase inhibitor vibralactone A[4a] and proteasome inhibitor salinosporamide A[4b] (Figure 1a). Efficient asymmetric methods to access this class of heterocyclic molecules continue to draw intense attention from both academic and industrial laboratories.[5] Most of the reactions reported to date rely on an intramolecular process (e.g., intramolecular aldol lactonization[6]) and/or start with optically enriched starting materials.[7] Intermolecular reactions starting with simple achiral substrates are more desired, but unfortunately much less developed (Figure 1b). In this regard, Romo and co-workers[8a] have reported a chiral-isothiourea-catalyzed intermolecular Michael/aldol/β-lactonization sequence to form cyclopentane-fused β-lactones involving an α,β-unsaturated acyl ammonium intermediate.[8] The carbocycle (cyclopentane) fused β-lactones have also been prepared via N-heterocyclic carbene[9,10] (abbreviated as carbene or NHC) mediated intermolecular reactions. The groups of Nair[11a] and Bode[11b,c] independently reported the reactions between enals and enones to afford cyclopentane-fused β-lactones, using the β-carbon nucleophilic reactivity of an enal, via homoenolate intermediates.[11] In these enal/enone reactions, the formed lactone moiety was typically unstable at room temperature and tended to undergo a decarboxylation process to eventually give cyclopentene as the final product.[11a,b] Lupton and co-workers reported NHC-catalyzed ring-opening of cyclopropanes to access highly functionalized cyclopentane-fused β-lactones.[12a,b] Studer and co-workers have disclosed the addition of the α-carbon atom of malonate to an α,β-unsaturated acyl azolium intermediate as a key step to synthesize a bicyclic β-lactone with two fully substituted stereocenters.[12c] Recently, Lupton and co-workers reported

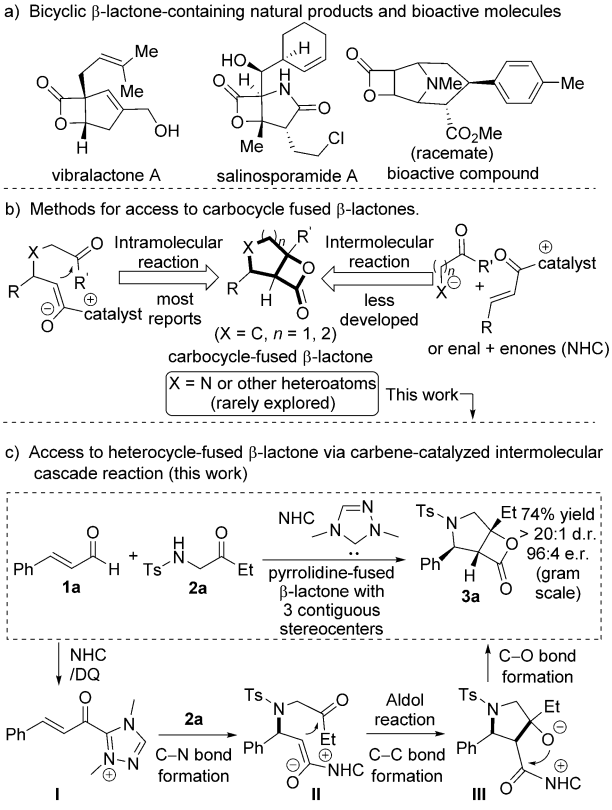


Figure 1. Access to bicyclic β-lactones. Ts = 4-toluenesulfonyl.

[*] X. Wu, L. Hao, Y. Zhang, M. Rakesh, R. N. Reddi, Prof. Dr. Y. R. Chi
Division of Chemistry & Biological Chemistry
School of Physical & Mathematical Sciences
Nanyang Technological University
Singapore 637371 (Singapore)
E-mail: robinchi@ntu.edu.sg
Prof. Dr. S. Yang, Prof. Dr. B.-A. Song, Prof. Dr. Y. R. Chi
Laboratory Breeding Base of Green Pesticide and Agricultural Bioengineering, Key Laboratory of Green Pesticide and Agricultural Bioengineering, Ministry of Education, Guizhou University
Huaxi District, Guiyang 550025 (China)

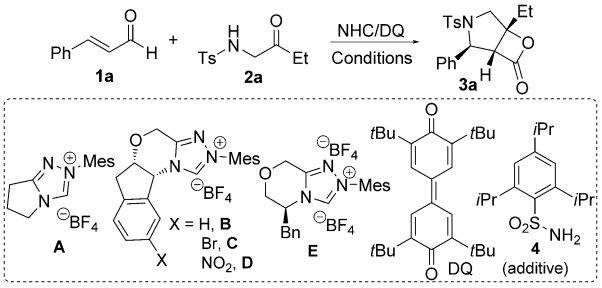
Supporting information for this article can be found under: http://dx.doi.org/10.1002/anie.201700045.

a [4+2] annulation, using donor-acceptor cyclobutane, to generate cyclohexyl β-lactones.[12d]

Herein we demonstrate a new method for asymmetric catalytic synthesis of bicyclic β-lactones (Figure 1c). In addition to the β-lactone moiety, our method constructs a new C–N bond to form a fused pyrrolidine ring. Our reaction employs readily available enals (e.g., **1a**) and amino ketones (e.g., **2a**) as the starting materials. The key mechanistic steps include intermolecular addition of a nitrogen nucleophile[13] to the unsaturated acyl azolium intermediate **I**,[14] followed by an aldol (**II**) and lactonization process (**III**[9,15]; see the Supporting Information for a complete catalytic cycle). The reactivity of the nitrogen atom in **2a** is modulated by the Ts group and the alkyl moiety to facilitate the challenging intermolecular aza-Michael addition (**I**→**II**). The pyrrolidine-fused β-lactone products (e.g., **3a**), bearing three contiguous stereogenic centers, including one quaternary carbon center, are obtained in good yields and excellent stereoselectivities.

We chose a readily available enal (**1a**) and α-amino ketone (**2a**) as the starting materials (Table 1). Ye and coworkers[16] previously used similar α-amino ketones as substrates in NHC catalysis, in which the α-carbon atom of the ketone behaves as a nucleophilic center to form a C–C bond. Key results in searching for suitable reaction conditions, by using 3,3′,5,5′-tetra-*tert*-butyldiphenoquinone (DQ) as an oxidant as pioneered by Studer et al.,[14a–c] are summarized in Table 1. The use of the triazolium NHC catalyst **A**[17a] led to the formation of desired product **3a** with 40% yield. Among the amino-indanol-derived NHCs,[17b,c] the nitro-substituted catalyst **D** afforded the desired lactone **3a** in moderate yield and 87:13 e.r. (entry 4). The use of the catalyst **E**[17d] gave **3a** with excellent yield, albeit in a much lower e.r. value (entry 5). Switch of base to Cs_2CO_3 led to an improved yield and e.r. value (entry 6). The use of $CHCl_3$ as a solvent provided a slight, while consistent improvement, of the e.r. value (from 90:10 to 93:7 e.r., entries 6 and 7). Unexpectedly, a slightly better e.r. value (95:5 e.r.) was observed when we used an impure sample of **2a** (containing $TsNH_2$ as the impurity). This observation inspired us to screen several additives (entries 8–9; see Table S3 in the Supporting Information) with the hope to get better enantioselectivity. We then found that the employment of the sulfonyl amide **4** (10 mol%) as an additive improved the reaction e.r. value (96:4 e.r., entry 9). However, the exact role of this additive remains unclear at this point. Finally, by increasing the loadings of **1a** (from 1.3 to 1.5 equiv) and the oxidant (from 1.2 to 1.4 equiv), **3a** was obtained in an acceptable yield (74%) with excellent diastereoselectivity (d.r. > 20:1) and 96:4 e.r. (entry 10).

Table 1: Screening of reaction conditions for the reaction of **1a** with **2a**.[a]



Entry	NHC	Base	Solvent	Yield [%][b]	e.r.
1	**A**	K_2CO_3	CH_2Cl_2	40	–
2	**B**	K_2CO_3	CH_2Cl_2	43	71:29
3	**C**	K_2CO_3	CH_2Cl_2	50	83:17
4	**D**	K_2CO_3	CH_2Cl_2	48	87:13
5	**E**	K_2CO_3	CH_2Cl_2	85	34:66
6	**D**	Cs_2CO_3[c]	CH_2Cl_2	61	90:10
7	**D**	Cs_2CO_3[c]	$CHCl_3$	64	93:7
8[d]	**D**	Cs_2CO_3[c]	$CHCl_3$	61	95:5
9[e]	**D**	Cs_2CO_3[c]	$CHCl_3$	65	96:4
10[f]	**D**	Cs_2CO_3[c]	$CHCl_3$	76 (74)	96:4

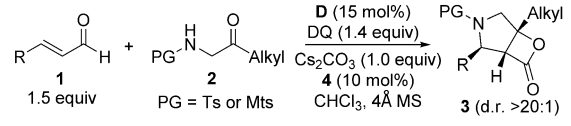
[a] Reaction conditions: **1a** (0.065 mmol, 1.3 equiv), **2a** (0.05 mmol, 1.0 equiv), NHC (15 mol%), K_2CO_3 (1.5 equiv), DQ (1.2 equiv), and 4 Å M.S. (50 mg) in solvent (0.05 M) at RT for 20 h. [b] Yields determined by NMR analysis with an internal standard. Yield of isolated product given within parentheses and is based on **2a**. [c] 1.0 equiv of Cs_2CO_3 was used instead. [d] 10 mol% of $TsNH_2$ was added. [e] 10 mol% of **4** was added. [f] 10 mol% of **4**, 1.5 equiv of **1a** and 1.4 equiv of DQ were used. Mes = 2,4,6-trimethylphenyl, M.S. = molecular sieves.

With acceptable reaction conditions in hand, we next investigated the generality of the reaction. Initially, we examined the scope of β-aryl and β-alkyl enals in the cascade process by using **2a** as a model substrate (Table 2). Various substituents and substitution patterns on the β-phenyl ring of enals were well tolerated to give the products with acceptable yields and good e.r. values (**3a–l**). Enals bearing readily transferrable functional units, such as Br (**3d**) and a carboxylic ester (**3l**) unit, were also used to give the corresponding β-lactones. The β-phenyl unit of **1a** could be replaced with heteroaryl substituents, such as furyl (**3m**) and pyridinyl units (**3n**). Additionally, β-alkyl enals were also screened in our approach (**3o–q**). In these reactions using β-alkyl enals, the use of an amino ketone protected with a slightly bulkier Mts (2,4,6-trimethylbenzenesulfonyl) group provided the lactone adduct **3p** with a slightly higher e.r. value than that using the Ts-protected amino ketone substrate (**3o**).

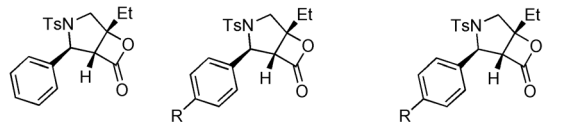
We next studied the scope with respect to the amino ketones by using **1a** as the model enal substrate (Table 2). The ethyl unit of **2a** could be replaced with a methyl (**3r**), isopropyl (**3s**), *n*-butyl (**3t**), benzyl (**3u**), and cyclohexyl unit (**3v**). As a technical note, when the amino ketone substrate bearing a relatively bulky isopropyl unit was used under the standard reaction conditions with **D** as the NHC catalyst, the product **3s** was obtained in low yield (29%). In this case, the use of **E** as the NHC catalyst promoted the formation of **3s** with 81% yield and 93:7 e.r. An acetal group in the amino ketone substrate was tolerated in our reaction as well (**3w**).

When α-amino ketones with aryl substituents were employed, the use of the catalyst *ent*-**B** gave better yields compared to that of **D** (see Table S4; Scheme 1a). In these cases, the initially formed bicyclic β-lactones underwent a spontaneous decarboxylation[11a,b] to form the corresponding 3-pyrroline products (**5a–d**) with good yields and excellent e.r. values. When these reactions were carried out at room temperature, a side adduct, **7** (approximately 10% yield), resulted from the reaction of the α-carbon atom of the ketone, as previously reported by Ye[16] (Scheme 1b). This

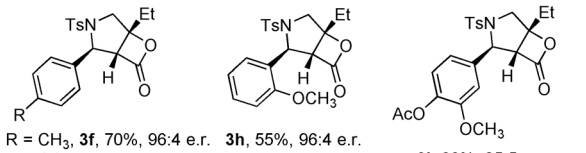
Table 2: Substrate scope.[a]



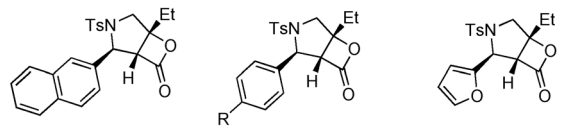
Variation of aldehyde **1** (with **2a** as the model amino ketone)



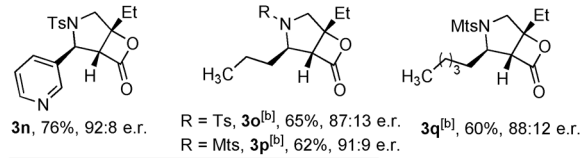
3a, 74%, 96:4 e.r. R = F, **3b**, 75%, 95:5 e.r. R = Cl, **3c**, 80%, 96:4 e.r. R = Br, **3d**, 74%, 95:5 e.r. R = NO_2, **3e**, 74%, 90:10 e.r.



R = CH_3, **3f**, 70%, 96:4 e.r. R = OCH_3, **3g**, 67%, 98:2 e.r. **3h**, 55%, 96:4 e.r. **3i**, 66%, 95:5 e.r.

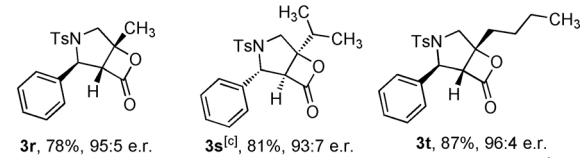


3j, 70%, 96:4 e.r. (CCDC 1518922) R = OAllyl, **3k**, 55%, 99:1 e.r. R = CO_2CH_3, **3l**, 71%, 98:2 e.r. **3m**, 45%, 98:2 e.r.

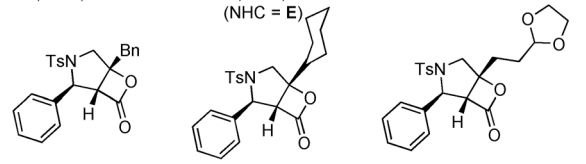


3n, 76%, 92:8 e.r. R = Ts, **3o**[b], 65%, 87:13 e.r. R = Mts, **3p**[b], 62%, 91:9 e.r. **3q**[b], 60%, 88:12 e.r.

Variation of ketone **2** (with **1a** as the model enal)



3r, 78%, 95:5 e.r. **3s**[c], 81%, 93:7 e.r. (NHC = **E**) **3t**, 87%, 96:4 e.r.

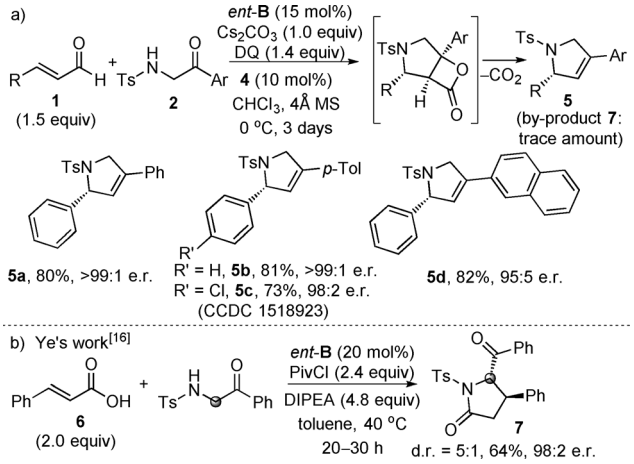


3u, 44%, 91:9 e.r. **3v**, 64%, 98:2 e.r. **3w**, 73%, 97:3 e.r.

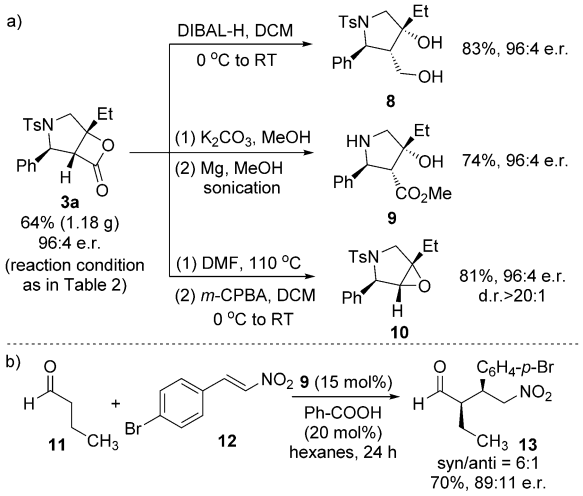
[a] Reaction conditions: **1** (1.5 equiv), **2** (0.10 mmol, 1.0 equiv), **D** (15 mol%), Cs_2CO_3 (1.0 equiv), **4** (10 mol%), DQ (1.4 equiv), and 4 Å M.S. (100 mg) in $CHCl_3$ (0.05 M) at RT for 20 h. Yields (after SiO_2 chromatography purification) based on **2**. [b] 2.0 equiv of enal **1** was used, and reaction was carried out at 40 °C. [c] Catalyst **E** was used instead of **D**. Mts = 2,4,6-trimethylbenzenesulfonyl.

side reaction was negligible when the reaction temperature was decreased to 0 °C (see Table S4).

Our cascade approach is amenable to gram-scale synthesis, with the formation of the β-lactone **3a** (1.18 g) in 64% yield and 96:4 e.r. (Scheme 2a). The scale-up of the reaction (using reaction conditions as in Table 2 without further optimization) led to a small drop in yield (from 74% to 64%) without loss in the e.r. values. The optically enriched pyrrolidine-fused β-lactone products obtained in our catalytic reaction can readily undergo further transformations. For



Scheme 1. Examples of α-amino aryl ketone substrates. DIPEA = diisopropylethylamine, Piv = pivaloyl.



Scheme 2. Synthetic transformations and catalytic applications of the products. DCM = dichloromethane, DIBAL-H = diisobutylaluminum hydride, DMF = *N*,*N*-dimethylformamide.

example, the lactone unit of **3a** was subjected to DIBAL-H reduction to furnish the corresponding diol **8** in 83% yield without erosion of the e.r. value. The Ts group on the nitrogen atom of **3a** was removed with Mg/MeOH after mild alcoholysis to afford the β-proline methyl ester **9** in 74% yield and 96:4 e.r. A preliminary application of **9** as an organocatalyst revealed that **9** could catalyze the Michael addition[18] of an aldehyde (**11**) to a nitroalkene (**12**) to afford the adduct **13** with 70% yield and a promising enantioselectivity (ca. 89:11 e.r.) without any optimizations (Scheme 2b). Decarboxylation of **3a** followed by an epoxidation reaction using *m*-CPBA gave the bicyclic epoxide **10** with 81% overall yield and 96:4 e.r. The oxabicyclic structure of **10** is commonly found as a core moiety in numerous antibiotic molecules and natural products such as (+)-epogymnolactam.[19]

In summary, we have developed a highly efficient organic catalytic method for rapid access to pyrrolidine-fused β-lactones. The reaction starts with a challenging intermolecular addition of a nitrogen nucleophile to the catalytically

generated unsaturated acyl azolium intermediate as a key step to form a new C–N bond. Direct asymmetric construction of a C–N bond to the β-carbon atom of the carbonyl compound is a most effective method to prepare non-natural amino-acid derivatives and N-heterocycles. Our carbene-catalyst-enabled asymmetric C–N, C–C, and C–O bond-forming cascade readily affords bicyclic pyrrolidine-fused β-lactones with good yields and excellent stereoselectivities. Mechanistically, this study provides insights in modulating the reactivities of nitrogen atoms and other heteroatoms in asymmetric reactions mediated by carbene catalysts. Further reaction development and evaluation of the bioactivity of pyrrolidine-fused β-lactones are in progress in our laboratory.

Acknowledgments

We acknowledge financial support by the National Natural Science Foundation of China (No. 21132003; No. 21472028), Singapore National Research Foundation (NRF-NRFI2016-06), the Ministry of Education of Singapore (MOE2013-T2-2-003; MOE2016-T2-1-032), Nanyang Technological University (NTU, Singapore), China's Ministry of Education, Thousand Talent Plan, Guizhou Province Returned Oversea Student Science and Technology Activity Program, Science and Technology of Guizhou Province, and Guizhou University.

Conflict of interest

The authors declare no conflict of interest.

Keywords: heterocycles · lactones · N-heterocyclic carbenes · organocatalysis · reaction mechanisms

[1] a) D. O'Hagan, *Nat. Prod. Rep.* **2000**, *17*, 435; b) P. M. Dewick, *Medicinal Natural Products: A Biosynthetic Approach*, Wiley, New York, **2002**, p. 292; c) L. Szabados, A. Savoure, *Trends Plant Sci.* **2010**, *15*, 89.

[2] For reviews on β-lactone-containing natural products: a) A. Pommier, J. M. Pons, *Synthesis* **1995**, 729; b) C. Lowe, J. C. Vederas, *Org. Prep. Proced. Int.* **1995**, *27*, 305.

[3] a) J. Taunton, J. L. Collins, S. L. Schreiber, *J. Am. Chem. Soc.* **1996**, *118*, 10412; b) X. Shen, A. S. Wasmuth, J. Zhao, C. Zhu, S. G. Nelson, *J. Am. Chem. Soc.* **2006**, *128*, 7438; c) V. C. Purohit, A. S. Matla, D. Romo, *J. Am. Chem. Soc.* **2008**, *130*, 10478; d) J. Douglas, J. E. Taylor, G. Churchill, A. M. Z. Slawin, A. D. Smith, *J. Org. Chem.* **2013**, *78*, 3925; e) L. R. Rieth, D. R. Moore, E. B. Lobkovsky, G. W. Coates, *J. Am. Chem. Soc.* **2002**, *124*, 15239.

[4] a) D.-Z. Liu, F. Wang, T.-G. Liao, J.-G. Tang, W. Steglich, H.-J. Zhu, J.-K. Liu, *Org. Lett.* **2006**, *8*, 5749; b) R. H. Feling, G. O. Buchanan, T. J. Mincer, C. A. Kauffman, P. R. Jensen, W. Fenical, *Angew. Chem. Int. Ed.* **2003**, *42*, 355; *Angew. Chem.* **2003**, *115*, 369; c) L. R. Dick, A. A. Cruikshank, L. Grenier, F. D. Melandri, S. L. Nunes, R. L. Stein, *J. Biol. Chem.* **1996**, *271*, 7273; d) L. Zhao, K. M. Johnson, M. Zhang, J. Flippen-Anderson, A. P. Kozikowski, *J. Med. Chem.* **2000**, *43*, 3283.

[5] a) K. N. Van, L. C. Morrill, A. D. Smith, D. Romo in *Lewis Base Catalysis in Organic Synthesis* (Eds.: E. Vedejs, S. E. Denmark), Wiley-VCH, Weinheim, **2016**, p. 527; b) H. Nguyen, S. Oh, H. Henry-Riyad, D. Sepulveda, D. Romo, *Org. Synth.* **2011**, *88*, 121.

[6] For Romo's pioneering work, see: a) G. S. Cortez, R. L. Tennyson, D. Romo, *J. Am. Chem. Soc.* **2001**, *123*, 7945; b) S. H. Oh, G. S. Cortez, D. Romo, *J. Org. Chem.* **2005**, *70*, 2835; c) G. Liu, D. Romo, *Org. Lett.* **2009**, *11*, 1143; d) C. A. Leverett, V. C. Purohit, D. Romo, *Angew. Chem. Int. Ed.* **2010**, *49*, 9479; *Angew. Chem.* **2010**, *122*, 9669; e) C. A. Leverett, V. C. Purohit, A. G. Johnson, R. L. Davis, D. J. Tantillo, D. Romo, *J. Am. Chem. Soc.* **2012**, *134*, 13348.

[7] a) L. R. Reddy, E. J. Corey, *Org. Lett.* **2006**, *8*, 1717; b) D. K. Mohapatra, D. Mondal, R. G. Gonnade, M. S. Ghorghade, M. K. Gurjar, *Tetrahedron Lett.* **2006**, *47*, 6031; c) K. Eto, M. Yoshino, K. Takahashi, J. Ishihara, S. Hatakeyama, *Org. Lett.* **2011**, *13*, 5398.

[8] a) G. Liu, M. E. Shirley, K. N. Van, R. L. McFarlin, D. Romo, *Nat. Chem.* **2013**, *5*, 1049; for selected reviews on isothiourea as a Lewis base catalyst, see: b) L. C. Morrill, A. D. Smith, *Chem. Soc. Rev.* **2014**, *43*, 6214; c) S. Vellalath, D. Romo, *Angew. Chem. Int. Ed.* **2016**, *55*, 13934; *Angew. Chem.* **2016**, *128*, 14138.

[9] NHC-catalyzed intramolecular reaction for the synthesis of bicyclic β-lactone has been pioneered by the groups of Scheidt and Lupton: a) M. Wadamoto, E. M. Phillips, T. E. Reynolds, K. A. Scheidt, *J. Am. Chem. Soc.* **2007**, *129*, 10098; b) E. M. Phillips, J. M. Roberts, K. A. Scheidt, *Org. Lett.* **2010**, *12*, 2830; c) D. T. Cohen, C. C. Eichman, E. M. Phillips, E. R. Zarefsky, K. A. Scheidt, *Angew. Chem. Int. Ed.* **2012**, *51*, 7309; *Angew. Chem.* **2012**, *124*, 7421; d) L. Candish, A. Levens, D. W. Lupton, *J. Am. Chem. Soc.* **2014**, *136*, 14397.

[10] Selected reviews on NHC catalysis: a) D. Enders, O. Niemeier, A. Henseler, *Chem. Rev.* **2007**, *107*, 5606; b) N. Marion, S. Díez-González, S. P. Nolan, *Angew. Chem. Int. Ed.* **2007**, *46*, 2988; *Angew. Chem.* **2007**, *119*, 3046; c) V. Nair, S. Vellalath, B. P. Babu, *Chem. Soc. Rev.* **2008**, *37*, 2691; d) A. T. Biju, N. Kuhl, F. Glorius, *Acc. Chem. Res.* **2011**, *44*, 1182; e) J. Douglas, G. Churchill, A. D. Smith, *Synthesis* **2012**, 2295; f) S. J. Ryan, L. Candish, D. W. Lupton, *Chem. Soc. Rev.* **2013**, *42*, 4906; g) M. N. Hopkinson, C. Richter, M. Schedler, F. Glorius, *Nature* **2014**, *510*, 485; h) D. M. Flanigan, F. Romanov-Michailidis, N. A. White, T. Rovis, *Chem. Rev.* **2015**, *115*, 9307; i) M. H. Wang, K. A. Scheidt, *Angew. Chem. Int. Ed.* **2016**, *55*, 14912; *Angew. Chem.* **2016**, *128*, 15134.

[11] a) V. Nair, S. Vellalath, M. Poonoth, E. Suresh, *J. Am. Chem. Soc.* **2006**, *128*, 8736; b) P.-C. Chiang, J. Kaeobamrung, J. W. Bode, *J. Am. Chem. Soc.* **2007**, *129*, 3520; c) J. Kaeobamrung, J. W. Bode, *Org. Lett.* **2009**, *11*, 677; for selected examples on homoenolate chemistry: d) C. Burstein, F. Glorius, *Angew. Chem. Int. Ed.* **2004**, *43*, 6205; *Angew. Chem.* **2004**, *116*, 6331; e) S. Sohn, E. L. Rosen, J. W. Bode, *J. Am. Chem. Soc.* **2004**, *126*, 14370; f) D. E. A. Raup, B. Cardinal-David, D. Holte, K. A. Scheidt, *Nat. Chem.* **2010**, *2*, 766; g) X.-D. Zhao, A. DiRocco, T. Rovis, *J. Am. Chem. Soc.* **2011**, *133*, 12466; h) H. Lv, W.-Q. Jia, L.-H. Sun, S. Ye, *Angew. Chem. Int. Ed.* **2013**, *52*, 8607; *Angew. Chem.* **2013**, *125*, 8769; i) X. Chen, X. Fang, Y. R. Chi, *Chem. Sci.* **2013**, *4*, 2613; j) C. Guo, M. Fleige, D. Janssen-Müller, C. G. Daniliuc, F. Glorius, *Nat. Chem.* **2015**, *7*, 842; k) S. Mukherjee, S. Mondal, A. P. Rajesh, G. Gonnadeb, A. T. Biju, *Chem. Commun.* **2015**, *51*, 9559; l) C. Guo, M. Fleige, D. Janssen-Müller, C. G. Daniliuc, F. Glorius, *J. Am. Chem. Soc.* **2016**, *138*, 7840.

[12] a) L. Candish, D. W. Lupton, *J. Am. Chem. Soc.* **2013**, *135*, 58; b) L. Candish, C. M. Forsyth, D. W. Lupton, *Angew. Chem. Int. Ed.* **2013**, *52*, 9149; *Angew. Chem.* **2013**, *125*, 9319; c) S. Bera, R. C. Samanta, C. G. Daniliuc, A. Studer, *Angew. Chem. Int. Ed.* **2014**, *53*, 9622; *Angew. Chem.* **2014**, *126*, 9776; d) A. Levens, A. Ametovski, D. W. Lupton, *Angew. Chem. Int. Ed.* **2016**, *55*, 16136; *Angew. Chem.* **2016**, *128*, 16370.

[13] a) H.-R. Zhang, Z.-W. Dong, Y.-J. Yang, P.-L. Wang, X.-P. Hui, *Org. Lett.* **2013**, *15*, 4750; b) X. Wu, B. Liu, Y. Zhang, M. Jeret, H. Wang, P. Zheng, S. Yang, B.-A. Song, Y. R. Chi, *Angew. Chem. Int. Ed.* **2016**, *55*, 12280; *Angew. Chem.* **2016**, *128*, 12468.

[14] a) J. Guin, S. De Sarkar, S. Grimme, A. Studer, *Angew. Chem. Int. Ed.* **2008**, *47*, 8727; *Angew. Chem.* **2008**, *120*, 8855; b) S. De Sarkar, A. Studer, *Angew. Chem. Int. Ed.* **2010**, *49*, 9266; *Angew. Chem.* **2010**, *122*, 9452; c) S. De Sarkar, S. Grimme, A. Studer, *J. Am. Chem. Soc.* **2010**, *132*, 1190; d) K. Zeitler, *Org. Lett.* **2006**, *8*, 637; e) S. J. Ryan, L. Candish, D. W. Lupton, *J. Am. Chem. Soc.* **2009**, *131*, 14176; f) Z.-Q. Rong, M.-Q. Jia, S.-L. You, *Org. Lett.* **2011**, *13*, 4080; g) A. G. Kravina, J. Mahatthananchai, J. W. Bode, *Angew. Chem. Int. Ed.* **2012**, *51*, 9433; *Angew. Chem.* **2012**, *124*, 9568; h) J. Mo, L. Shen, Y. R. Chi, *Angew. Chem. Int. Ed.* **2013**, *52*, 8588; *Angew. Chem.* **2013**, *125*, 8750; i) Z.-Q. Liang, D.-L. Wang, H.-M. Zhang, S. Ye, *Org. Lett.* **2015**, *17*, 5140; j) S. Bera, C. G. Daniliuc, A. Studer, *Org. Lett.* **2015**, *17*, 4940; k) G.-T. Li, Q. Gu, S.-L. You, *Chem. Sci.* **2015**, *6*, 4273; l) S. R. Yetra, S. Mondal, S. Mukherjee, R. G. Gonnade, A. T. Biju, *Angew. Chem. Int. Ed.* **2016**, *55*, 268; *Angew. Chem.* **2016**, *128*, 276; For reviews, see: m) S. De Sarkar, A. Biswas, R. C. Samanta, A. Studer, *Chem. Eur. J.* **2013**, *19*, 4664; n) J. Mahatthananchai, J. W. Bode, *Acc. Chem. Res.* **2014**, *47*, 696.

[15] For NHC-catalyzed [2+2] cycloadditions, see: a) L. He, H. Lv, Y.-R. Zhang, S. Ye, *J. Org. Chem.* **2008**, *73*, 8101; b) X.-N. Wang, P.-L. Shao, H. Lv, S. Ye, *Org. Lett.* **2009**, *11*, 4029; c) J. J. Douglas, G. Churchill, A. M. Z. Slawin, D. J. Fox, A. D. Smith, *Chem. Eur. J.* **2015**, *21*, 16354; d) A. T. Davies, A. M. Z. Slawin, A. D. Smith, *Chem. Eur. J.* **2015**, *21*, 18944.

[16] X.-Y. Chen, Z.-H. Gao, C.-Y. Song, C.-L. Zhang, Z.-X. Wang, S. Ye, *Angew. Chem. Int. Ed.* **2014**, *53*, 11611; *Angew. Chem.* **2014**, *126*, 11795.

[17] a) S. S. Sohn, J. W. Bode, *Org. Lett.* **2005**, *7*, 3873; b) J. R. Struble, J. W. Bode, *Org. Synth.* **2010**, *87*, 362; c) S. Kuwano, S. Harada, B. Kang, R. Oriez, Y. Yamaoka, K. Takasu, K. Yamada, *J. Am. Chem. Soc.* **2013**, *135*, 11485; d) I. Piel, M. Steinmetz, K. Hirano, R. Frohlich, S. Grimme, F. Glorius, *Angew. Chem. Int. Ed.* **2011**, *50*, 4983; *Angew. Chem.* **2011**, *123*, 5087.

[18] a) J. M. Betancort, C. F. Barbas III, *Org. Lett.* **2001**, *3*, 3737; b) Y. Hayashi, H. Gotoh, T. Hayashi, M. Shoji, *Angew. Chem. Int. Ed.* **2005**, *44*, 4212; *Angew. Chem.* **2005**, *117*, 4284.

[19] Y. Okado, K. Shigetomi, S. Mitsuhashi, M. Ubukata, *J. Antibiot.* **2015**, *68*, 721.

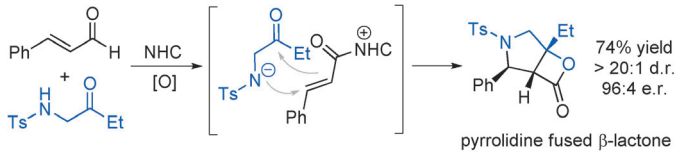
Manuscript received: January 3, 2017
Revised: February 12, 2017
Final Article published: ■■ ■■, ■■■■

Communications

Carbenes

X. Wu, L. Hao, Y. Zhang, M. Rakesh, R. N. Reddi, S. Yang, B.-A. Song, Y. R. Chi* ——— ■■■■–■■■■

Construction of Fused Pyrrolidines and β-Lactones by Carbene-Catalyzed C–N, C–C, and C–O Bond Formations



Fused: The challenging intermolecular addition of a nitrogen nucleophile to a catalytically generated unsaturated acyl azolium intermediate provides a highly efficient method for asymmetric access to pyrrolidine-fused β-lactones. The unique bicyclic β-lactone structure, bearing three contiguous stereogenic centers, is readily transformed into useful functional molecules such as amino catalysts. NHC = N-heterocyclic carbene.

